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Para-acyl-calix[9]arenes: synthesis and interfacial assembly

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Abstract The synthesis of a series of five *para*-acyl-calix[9]arenes has been achieved with total substitution as shown by MALDI-TOF mass spectrometry. All compounds form stable monolayers at the air–water interface, with apparent molecular areas between 200 and 330 $Å^2$.

Keywords Calix[n]arene · Calix[9]arene acylation · Langmuir · Monolayer · Supramolecular assembly

Introduction

The calix[n]arenes are amongst the most widely studied organic macrocyclic compounds [1]. Their *para*-position (upper rim) and the phenolic groups (lower rim) can be easily modified separately via simple chemical reactions [2]. Friedel–Crafts acylation at the para-position [3] gives access to amphiphilic derivatives in high yields [4]. *Para*-acyl-calix[4]arenes have shown self assembly properties, varying from solid-state nano-capsules, that can act as gas storage systems [5] and nano-reactors [6], through Langmuir monolayers able to interact with cations and anions [6], to solid lipid nanoparticles [7]. Investigations on chemistry and self-assembly properties of the *para*-acyl-calix[8]arenes were recently started [8]. Combinations of various functional groups on the phenolic face led to novel molecules building self-assembled structures, also showing interesting complexation capacities towards proteins [9]. As the biological activity of the calix[n]arenes generally increases with the size of the macrocyclic ring,[10, 11] while the interfacial properties vary widely with the size of the macrocycle, the synthesis and the study of self assembly properties of the higher calix[n]arenes is obviously of interest.

To obtain calix[9]arenes, two distinct strategies have been developed in the past. Dumazet et al. have reported the synthesis of para-tert-butylcalix[9]arene from 6 + 3 cyclisation reaction between linear phenolic oligomers (hypothesis of 100% linear hexamer) and a triphenolic unit (2,6-bis(5-tert-butylsalicyl)-4-tert-butylphenol) under basic conditions [12]. Stewart et al. also described an elegant approach via an acid-catalyzed process, using para-tert-butylphenol, s-trioxane as formaldehyde source and *p*-toluenesulfonic acid as the catalyst [13]. However, both methods involve tedious and time-consuming separation of the para-tert-butylcalix[9]arene from other by-products. The desired product is finally obtained after purification in very low yields (1%–8%). Consequently, few calix[9]arene derivatives are known. De-tert-butylation of calix[9]arene and modification of the upper rim by phenylazo groups was realized by Lamartine's group [14]. Gloede et al. have also reported the preparation of a bridged para-tert-butylcalix[9]arene triphosphate by reaction of para-tert-butylcalix[9]arene with PCl_5[15]. Similarly, few applications of calix[9]arene derivatives have been reported in the literature and only studies of the interactions between these compounds and ions have been reported. The calix[9]arenes complex lanthanides for example europium [15, 16] and have been used in the preparation of microsensors for copper detection [17]. The development of the calix[9]arene chemistry thus required an efficient route to para-tert-butylcalix[9]arene. This was achieved recently by Bew et al., who reported a suitable synthetic route using tin (IV) chloride, s-trioxane and para-tert-butylphenol with an

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acceptable yield (36%) and using an easy purification (flash chromatography) [18].

Experimental

General experimental details

NMR spectra were recorded on a Brucker spectrometer, 500 MHz for ^{1}H and 125 MHz for ^{13}C (TMS as internal standard, chemical shifts in ppm). Mass spectra (MALDI-TOF) were recorded on a Voyager DE-PRO instrument (Applied Biosystems). Langmuir isotherms were recorded on a NIMA 6010 film balance on pure water (>18 MΩ) at 20 °C, all isotherms were repeated at least three times, variability was less than 3% in all cases. Elemental analysis (C, H, N,) was carried out by the Service Central d'Analyse of the CNRS (Solaize). **1** was obtained according to described procedures [18].

Synthesis of ***2***

To a solution of **1** (0.800 g, 1 equiv.) in toluene (15 mL) were added aluminium trichloride (0.950 g, 13 equiv.) and phenol (0.098 g, 1.9 equiv.). The resultant solution was stirred under nitrogen at room temperature for 24 h, poured onto ice then stirred for 1 h. The organic phase was separated, concentrated under reduced pressure up to a volume of 10 mL and the product was finally precipitated from methanol (100 mL). The solid was filtered off, washed with MeOH (3 × 50 mL) and with Et_2O (3 × 50 mL) to give compound **2** as a cream powder.

^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm): 8.75 (bs, 9H, ArOH), 6.85 (d, 18H, $H_{méta}Ar$, J = 7.6 Hz), 6.85 (t, 9H, $H_{para}Ar$, J = 7.6 Hz), 7.88 (s, 18H, $H_{meta}Ar$), 3.88 ppm (s, 18H, Ar–CH_2–Ar). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm): 149.8 (CAr–OH), 126.2 ($C_{meta}Ar$), 125.7 (CAr–CH_2), 117.9 ($C_{para}Ar$), 28.6 (Ar–CH_2–Ar). MS (calculated): 977.4 (MALDI-TOF): 977.5 [**2** + Na^+]. mp >250 °C. Anal. calculated. (%) for $C_{62}H_{63}O_9$: C, 78.21; H, 6.67; O, 15.12. Found: C, 78.27, H, 6.34. Yield = 73%.

Synthesis of ***3a–3e***

Aluminium trichloride (23 equiv.) and the relevant acyl chloride (23 equiv.) were added under nitrogen to nitrobenzene (5 mL) and the mixture was stirred for 10 min. The solution became dark brown. **2** (1 equiv.) was then added. The resultant solution was stirred at room temperature for 24 h, then poured onto ice and stirred for 1 h to stop the reaction. The organic phase was extracted with chloroform (100 mL), washed with 1 M HCl (2 × 100 mL), brine (2 × 100 mL), water (100 mL) and dried over anhydrous $MgSO_4$. Chloroform was removed under reduced pressure, and the nitrobenzene distilled off under vacuum (10^{-2} Torr) to give a clear brown paste.

A hydrolysis reaction was realised on the product with 75 mL of a solution of KOH (10%) in ethanol/water (90:10) during 24 h at room temperature for **3a–c** and at 70 °C for **3d–e**. The ethanol was removed under reduced pressure. The product were precipitated with a solution of HCl 1 M (300 mL) and filtered. The resultant compounds were solubilised in chloroform (100 mL), washed with water (2 × 100 mL) and dried over anhydrous $MgSO_4$. Chloroform was removed under reduced pressure up to total volume of 20 mL. Compounds **3a–e** were finally obtained after precipitation from methanol (300 mL), filtration and *vacuum* drying.

Compound **3a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 10.05 (s, 9H, ArOH), 7.88 (s, 18H, $H_{meta}Ar$), 4.07 (br s, 18H, Ar–CH_2–Ar), 2.90 (t, 18H, CH_2CO), 1.69 (m, 18H, –CH_2–CH_2–CO), 1.34 (m, –$(CH_2)_2$–, 36H), 0.89 (t, CH_3–CH_2, 27H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 198.9 (C=O), 153.0 (CAr–OH), 132.0 (*C*Ar–C=O), 130.0 (CHAr), 127.5 (*C*Ar–CH_2), 38.5 (CO–*C*H_2), 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 24.4 (2× CH_2 and Ar–CH_2–Ar), 22.7 (*C*H_2–CH_3) 14.2 (CH_3). MS (Calculated): 1861.0, (MALDI-TOF): 1860.9 [**3a** + Na^+]. mp >250 °C. Elemental analysis: calculated. (%) $C_{116}H_{153}O_{18*}$3MeOH: C, 74.00; H, 8.61; O, 17.39. Found: C, 74.16, H, 8.47. Yield = 84%.

Compound **3b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 10.00 (s, 9H, ArOH), 7.88 (s, 18H, $H_{meta}Ar$), 4.06 (br s, 18H, Ar–CH_2–Ar), 2.90 (t, 18H, CH_2CO), 1.69 (m, 18H, –CH_2–CH_2–CO), 1.28 (m, –$(CH_2)_4$–, 72H), 0.88 (t, CH_3–CH_2, 27H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 199.0 (C=O), 153.1 (CAr–OH), 132.0 (*C*Ar–C=O), 130.0 (CHAr), 127.5 (*C*Ar–CH_2), 38.5 (CO–*C*H_2), 31.7, 29.7, 29.4, 29.2, 29.0, 24.5, 23.9 (4× CH_2 and Ar–CH_2–Ar), 22.6 (*C*H_2–CH_3) 14.1 (CH_3). MS (Calculated): 2113.3, (MALDI-TOF): 2113.8 [**3b** + Na^+]. mp >250 °C. Elemental analysis: calculated $C_{134}H_{189}O_{18*}$3MeOH: C, 75.34; H, 9.28; O, 15.38. Found: C, 75.51, H, 9.08. Yield = 67%.

Compound **3c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 10.07 (s, 9H, ArOH), 7.88 (s, 18H, $H_{meta}Ar$), 4.07 (br s, 18H, Ar–CH_2–Ar), 2.91 (t, 18H, CH_2CO), 1.69 (m, 18H, –CH_2–CH_2–CO), 1.27 (m, –$(CH_2)_6$–, 108H), 0.87 (t, CH_3–CH_2, 27H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 198.5 (C=O), 152.6 (CAr–OH), 131.7 (*C*Ar–C=O), 129.7 (CHAr), 127.1 (*C*Ar–CH_2), 38.1 (CO–*C*H_2), 31.5, 29.2, 29.1, 29.0, 24.1, 23.9 (6× CH_2 and Ar–CH_2–Ar), 22.4 (*C*H_2–CH_3) 13.8 (CH_3). MS (Calculated): 2365.6, (MALDI-TOF): 2365.5 [**3c** + Na^+]. mp >250 °C. Elemental analysis: calculated $C_{152}H_{225}O_{18*}$MeOH: C, 77.46; H, 9.73; O, 12.81 Found: C, 77.51, H, 9.61. Yield = 64%.

Compound **3d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 10.05 (s, 9H, ArOH), 7.87 (s, 18H, $H_{meta}Ar$), 4.06 (br s,

18H, Ar–CH_2–Ar), 2.90 (t, 18H, CH_2CO), 1.69 (m, 18H, –C*H*$_2$–CH_2–CO), 1.25 (m, –$(CH_2)_8$–, 144H), 0.87 (t, CH_3–CH_2, 27H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 199.1 (C=O), 153.2 (CAr–OH), 131.5 (*C*Ar–C=O), 130.2 (CHAr), 127.5 (*C*Ar–CH_2), 38.7 (CO–*C*H$_2$), 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 24.6, 24.1 (8× CH_2 and Ar–CH_2–Ar), 22.9 (*C*H$_2$–CH_3) 14.3 (CH_3). MS (Calculated): 2617.9, (MALDI-TOF): 2618.3 [**3d** + Na^+]. mp >250 °C. Elemental analysis: $C_{170}H_{261}O_{18*}$2MeOH: C, 77.75; H, 10.20; O, 12.04 Found: C, 77.74, H, 10.12. Yield = 80%.

Compound **3e**: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 10.05 (s, 9H, ArOH), 7.85 (s, 18H, H_{meta}Ar), 4.02 (br s, 18H, Ar–CH_2–Ar), 2.87 (t, 18H, CH_2CO), 1.66 (m, 18H, –C*H*$_2$–CH_2–CO), 1.22 (m, –$(CH_2)_{10}$–, 180H), 0.85 (t, CH_3–CH_2, 27H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 198.9 (C=O), 152.9 (CAr–OH), 132.0 (*C*Ar–C=O), 130.0 (CHAr), 127.4 (*C*Ar–CH_2), 38.5 (CO–*C*H$_2$), 32.0, 29.7, 29.6, 29.5, 29.4, 24.4, (10× CH_2 and Ar–CH_2–Ar), 22.7 (*C*H$_2$–CH_3) 14.2 (CH_3). MS (Calculated): 2871.1, (MALDI-TOF): 2870.1 [**3e** + Na^+]. mp >250 °C. Elemental analysis: calculated $C_{188}H_{297}O_{18}$: C, 79.36; H, 10.52; O, 10.12 Found: C, 79.42, H, 10.39. Yield = 77%.[1]

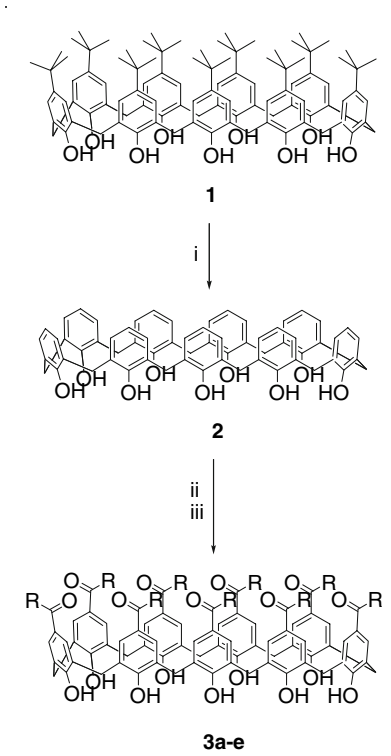
Results and discussion

The synthetic route to the *para*-acyl-calix[9]arenes is shown below in Scheme. 1. The complete removal of the *tert*-butyl groups is the key step and uses a modified version of the standard method [14], involving the use of toluene as solvent instead of 1,2-dichloroethane and a lower quantity of phenol (2 equiv. instead of 9 equiv.). By using these improved conditions, the yield of reaction increased from 46% to 73%. Physical data were in full agreement with the literature [14].

Para-acylation is carried out under Friedel–Crafts conditions as developed for the *para*-acyl-calix[8]arenes [8], in order to obtain total substitution at the *para*-position. Esterification of the phenolic groups occurs in some cases and the desired compounds are obtained after hydrolysis using ethanolic-potassium hydroxide either at room temperature or at 70 °C to complete the saponification reaction. Yields from the acylation steps are generally good, between 64% and 84%.

The ^{1}H NMR spectra show sharp signals at 4.07 ppm, typical of methylene protons of conformationally labile calix[n]arenes.

[1] It should be noted that for incomplete acylation, C,H analysis does not provide clear differences for up to 20% of underacylation, and that this is further complicated by the presence of solvents such as methanol.



Scheme 1 Synthetic route to the amphiphilic *para*-acyl-calix[9]arenes, **3a–e** (**a** R = C_5H_{11}, **b** R = C_7H_{15}, **c** R = C_9H_{19}, **d** R = $C_{11}H_{23}$, **e** R = $C_{13}H_{27}$). Reagents and conditions: (i) $AlCl_3$, Toluene, r.t, overnight; (ii) $AlCl_3$, RCOCl, Nitrobenzene, r.t, 2 days; (iii) EtOH/KOH r.t or 70 °C

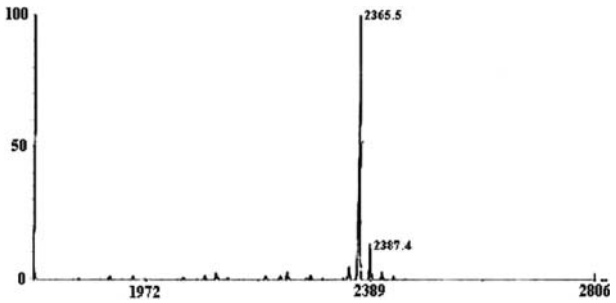


Fig. 1 MALDI TOF mass spectra of the amphiphilic *para*-decanoyl-calix[9]arene **3c**, (M range 1,700–2800)

After saponification, the MALDI TOF mass spectra show only peaks arising from the fully substituted products, as seen in Fig. 1.

In cases of over or under acylation of **2**, the corresponding peaks were clearly observable, as we have previously shown for the analogous *para*-acyl-calix[8]arene derivatives.[8] We consider MALDI- TOF to be the methodology of choice for confirming the degree of substitution of *para*-acyl-calix[9]arenes.

All the derivatives form stable monolayers at the air–water interface. The compression isotherms and summaries

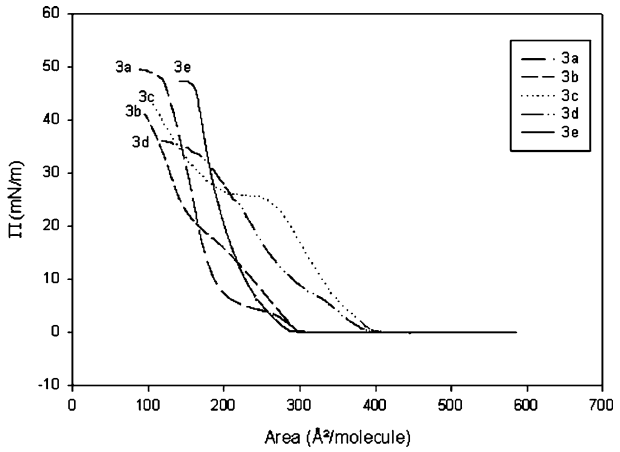


Fig. 2 Surface pressure-molecular area isotherms of the amphiphilic *para*-acyl-calix[9]arenes **3a–e** at air–water interface at 20 °C

of the isotherm data are given below in Fig. 2 and Tables 1 and 2.

The interfacial behaviour of the *para*-acyl-calix[9]arene derivatives may be divided into three groups depending on the length of the *para*-acyl chains. Hence the limiting molecular areas vary from ca. 200 $Å^2$ for **3a** and **3b** which have C6 and C8 chains to 280–330 $Å^2$ for **3c** and **3d**. Surprisingly the observed limiting area is 220 $Å^2$ for **3e** with an acyl chain length of 14 carbon atoms. Except for **3e**, the area increases with the acyl chain length. All the compounds except **3d** show surface pressures at the collapse in excess of 40 mN/m, however for **3d** it is possible that the plateau at 34 mN/m is associated with a phase change and not with a monolayer collapse.

All the isotherms, except for **3e** show clear phase changes, as demonstrated by the formation of plateau regions in the isotherms. From the compressibility modulii, Table 2, these phase changes are associated with passage from an expanded liquid to a condensed liquid phase. The surface pressures at which these phase changes occurs increases with the length of the acyl chain. In the case of **3e** there is apparently no formation of a liquid expanded phase, this may arise from a rigidification of the chains and a more perpendicular to the air–water interface orientation,

Table 1 Isotherm data for the *para*-acyl-calix[9]arene derivatives

	Π coll (mN/m)	A coll ($Å^2$)	A_{lim} ($Å^2$)	A_0 ($Å^2$)	A_1 ($Å^2$)
3a	48	121	200	304	291
3b	>42	<94	206	306	291
3c	>42	<104	282	407	388
3d	34	167	334	392	378
3e	47	162	220	295	278

Π_{coll} is the collapse pressure, A_{coll} is the area at the collapse, A_{lim} is the extrapolated molecular area, A_0 is the apparent molecular area at $\Pi = 0$ mN/m, A_1 is the apparent molecular area at $\Pi = 1$mN/m.

Table 2 Compressibility modulii of the monolayer formed by *para*-acyl-calix[9]arenes, **3a–e**

	Phase change ($Å^2$/molecule)	Cs^{-1} (mN/m)
3a	270	26.9
	208	108.3
3b	240	46.8
	142	108.9
3c	262	78.9
	198	77.1
3d	167	67.5
3e		124.0

which is in agreement with the lower limiting molecular area observed for this compound.

Conclusion

A series of five new *para*-acyl-calix[9]arenes have been synthesized in good yields and total upper rim substitution was demonstrated using MALDI-TOF mass spectrometry. All compounds form stable monolayers at the air–water interface and present different interfacial behavior as a function of the length of the acyl chains. Their ability to form stable nanoparticles is currently under study.

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